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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Jan 25  BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS  3  Jan 25  Searching with the P indicator for Preparations
 NEWS  4  Jan 29  FSTA has been reloaded and moves to weekly updates
 NEWS  5  Feb 01  DKILIT now produced by FIZ Karlsruhe and has a new update
                  frequency
 NEWS  6  Feb 19  Access via Tymnet and SprintNet Eliminated Effective 3/31/02
 NEWS  7  Mar 08  Gene Names now available in BIOSIS
 NEWS  8  Mar 22  TOXLIT no longer available
 NEWS  9  Mar 22  TRCTHERMO no longer available
 NEWS 10  Mar 28  US Provisional Priorities searched with P in CA/CAplus
                  and USPATFULL
 NEWS 11  Mar 28  LIPINSKI/CALC added for property searching in REGISTRY
 NEWS 12  Apr 02  PAPERCHEM no longer available on STN.  Use PAPERCHEM2 instead.

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> s Pinsky D?/au or Stern D?/au or Schmidt A?/au or Rose E?/au or Solomon R?/au
L1        12014 PINSKY D?/AU OR STERN D?/AU OR SCHMIDT A?/AU OR ROSE E?/AU OR
                SOLOMON R?/AU

=> s l1 and ( factor (1N) IX)
L2           99 L1 AND (FACTOR (1N) IX)

=> s l2 (P) (factor (1N) IXai)
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L6  (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L7  (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L8  (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L9  (P) '
L3           13 L2 (P) (FACTOR (1N) IXAI)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            6 DUP REM L3 (7 DUPLICATES REMOVED)

=> dis l4 1-6 ibib abs

L4   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         1999:443190  CAPLUS
DOCUMENT NUMBER:          131:208823
TITLE:                    Targeted inhibition of intrinsic coagulation limits
                          cerebral injury in stroke without increasing
                          intracerebral hemorrhage
AUTHOR(S):                Choudhri, Tanvir F.; Hoh, Brian L.; Prestigiacomo,
                          Charles J.; Huang, Judy; Kim, Louis J.; Schmidt,
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Ann Marie; Kisiel, Walter; Connolly, E. Sander, Jr.; **Pinsky, David J.**
CORPORATE SOURCE: Department of Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, NY, 10032, USA
SOURCE: J. Exp. Med. (1999), 190(1), 91-99
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Agents that restore vascular patency in stroke also increase the risk of intracerebral hemorrhage (ICH). As Factor IXa is a key intermediary in the intrinsic pathway of coagulation, targeted inhibition of Factor IXa-dependent coagulation might inhibit microvascular thrombosis in stroke without impairing extrinsic hemostatic mechanisms that limit ICH. A competitive inhibitor of native Factor IXa for assembly into the intrinsic Factor X activation complex, **Factor IXai**, was prepd. by covalent modification of the Factor IXa active site. In a modified cephalin clotting time assay, in vivo administration of **Factor IXai** caused a dose-dependent increase in time to clot formation (3.6-fold increase at the 300 .mu.g/kg dose compared with vehicle-treated control animals, $P < 0.05$). Mice given **Factor IXai** and subjected to middle cerebral artery occlusion and reperfusion demonstrated reduced microvascular fibrin accumulation by immunoblotting and immunostaining, reduced 111In-labeled platelet deposition (42% decrease, $P < 0.05$), increased cerebral perfusion (2.6-fold increase in ipsilateral blood flow by laser doppler, $P < 0.05$), and smaller cerebral infarcts than vehicle-treated controls (70% redn., $P < 0.05$) based on tri-Ph tetrazolium chloride staining of serial cerebral sections. At therapeutically EDs, **Factor IXai** was not assocd. with increased ICH, as opposed to tissue plasminogen activator (tPA) or heparin, both of which significantly increased ICH. **Factor IXai** was cerebroprotective even when given after the onset of stroke, indicating that microvascular thrombosis continues to evolve (and may be inhibited) even after primary occlusion of a major cerebrovascular tributary.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:208429 CAPLUS
DOCUMENT NUMBER: 128:266260
TITLE: Methods using selectin antagonists, carbon monoxide, and inactivated **factor IX** for treating an ischemic disorder and improving stroke outcome
INVENTOR(S): **Pinsky, David J.**; **Stern, David**; **Schmidt, Ann Marie**; **Rose, Eric A.**; Connoly, E. Sander; **Solomon, Robert A.**; Prestigiacomo, Charles J.
PATENT ASSIGNEE(S): Trustees of Columbia University In the City of New York, USA; Pinsky, David J.; Stern, David; Schmidt, Ann Marie; Rose, Eric A.; Connoly, E. Sander; Solomon, Robert A.; Prestigiacomo, Charles J.
SOURCE: PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9813058	A1	19980402	WO 1997-US17229	19970925
W: AU, CA, JP, MX, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9745942	A1	19980417	AU 1997-45942	19970925
EP 951292	A1	19991027	EP 1997-944453	19970925
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001501612	T2	20010206	JP 1998-515905	19970925
US 6315995	B1	20011113	US 1998-53871	19980401
US 6316403	B1	20011113	US 1999-269426	19990625

PRIORITY APPLN. INFO.: US 1996-721447 A2 19960927
WO 1997-US17229 W 19970925

AB A method for treating an ischemic disorder in a subject comprises administering to the subject a pharmaceutically acceptable form of a selectin antagonist in a sufficient amt. over a sufficient time to prevent white blood cell accumulation. Also provided is a method for treating an ischemic disorder in a subject which comprises administering to the subject carbon monoxide gas in a sufficient amt. over a sufficient time. Further provided is a method for treating an ischemic disorder in a subject which comprises administering to the subject a pharmaceutically acceptable form of inactivated **Factor IX** in a sufficient amt. over a sufficient time to inhibit coagulation.

L4 ANSWER 3 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998024415 MEDLINE
DOCUMENT NUMBER: 98024415 PubMed ID: 9360098
TITLE: Selective anticoagulation with active site blocked factor IXa in synthetic patch vascular repair results in decreased blood loss and operative time.
AUTHOR: Spanier T B; Oz M C; Madigan J D; **Rose E A**; **Stern D M**; Nowygrod R; **Schmidt A M**
CORPORATE SOURCE: Department of Surgery, Columbia University College of Physicians & Surgeons, New York, USA.
CONTRACT NUMBER: AG00602 (NIA)
HL21007 (NHLBI)
HL35246 (NHLBI)
SOURCE: ASAIO JOURNAL, (1997 Sep-Oct) 43 (5) M526-30.
Journal code: BBH; 9204109. ISSN: 1058-2916.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980115

AB Heparin has been the mainstay of anti thrombic therapy in arterial repair procedures. With increasing use of synthetic patch angioplasty (polytetrafluoroethylene [PTFE] or Dacron, Medical Products, Flagstaff, AZ) to improve long-term patency and limit aneurysmal dilation, however,

the use of heparin has been associated with excessive needle hole bleeding, resulting in time delay in the operating room to achieve hemostasis, as well as clinically significant blood loss. Because of the multiple sites of action of heparin in the coagulation cascade, both intravascular (desired effect) and extravascular (untoward side effect) hemostasis are impaired. The authors therefore tested the hypothesis that selective inhibition of intravascular coagulation, without significant impairment of extravascular hemostasis, would prevent clotting intraluminally while preserving hemostasis at the suture line of the patch graft. The unique position of **factor IX**/IXa in the coagulation cascade renders its inhibition an ideal target in this setting. The authors prepared active site blocked **factor** IXa (**IXai**) using dansyl-Glu-Gly-Arg chloromethylketone, and tested this hypothesis in a New Zealand rabbit aortotomy model with PTFE patch closure using either heparin (25 i.u./kg; n = 16) or IXai (300 micrograms/kg; n = 21). The infrarenal aorta was identified and isolated, the anti coagulant infused, aortic cross clamp placed, and aortotomy repaired with a 2 x 6 mm PTFE patch. After cross-clamp removal, blood loss was measured and time to hemostasis was recorded. Compared with heparin, IXai resulted in significantly reduce blood loss (6.97 +/- 4.4 g vs 2.72 +/- 2.51 g, respectively, $p < 0.008$), and time to hemostasis (2.94 +/- 0.77 min vs 2.0 +/- 0.63 min, respectively, $p < 0.003$). To assess long-term patency and thrombosis, 12 rabbits (given heparin; n = 6 and IXai; n = 6) were observed for up to 2 months post-operatively. No differences were observed between rabbits treated with heparin or IXai; 100% of the grafts were patent with no differences in degree of intimal hyperplasia by histologic analysis. Together, these data suggest that use of IXai in PTFE vascular repair will safely allow realization of the benefits of long-term patency and decreased aneurysmal dilatation, while eliminating the intraoperative morbidity of needle hole bleeding.

L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:710255 CAPLUS
DOCUMENT NUMBER: 127:355173
TITLE: Active site-blocked **factor** IXa (**IXai**): a novel selective anticoagulant for use in cardiopulmonary bypass
AUTHOR(S): Spanier, Talia B.; Oz, Mehmet C.; Minanov, Oktavijan P.; **Stern, David M.**; **Rose, Eric A.**; **Schmidt, Ann Marie**
CORPORATE SOURCE: Department of Surgery, Columbia College of Physicians and Surgeons, New York, NY, USA
SOURCE: Surg. Forum (1997), 48, 259-261
CODEN: SUFOAX; ISSN: 0071-8041
PUBLISHER: American College of Surgeons
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We hypothesized that blockade of **factor IX**, because of its unique position in the intrinsic coagulation cascade, would selectively inhibit intravascular cardiopulmonary bypass circuit, contact-mediated thrombosis, while preserving extravascular, tissue factor-mediated hemostasis. This targeted antithrombotic strategy would allow cardiopulmonary bypass without heparin and eliminate the need for pharmacol. reversal. Using a baboon model of cardiopulmonary bypass, we have demonstrated that prevention of assembly of factor IXa into the factor X activation complex on an appropriate cell surface effectively prevents thrombosis in the intravascular space and extracorporeal circulation.

L4 ANSWER 5 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 91268089 MEDLINE
DOCUMENT NUMBER: 91268089 PubMed ID: 2050700
TITLE: Activation of the coagulation mechanism on tumor necrosis factor-stimulated cultured endothelial cells and their extracellular matrix. The role of flow and **factor IX**/IXa.
AUTHOR: Tijburg P N; Ryan J; **Stern D M**; Wollitzky B; Rimon S; Rimon A; Handley D; Nawroth P; Sixma J J; de Groot P G
CORPORATE SOURCE: Department of Hematology, University Hospital, Utrecht, The Netherlands.
CONTRACT NUMBER: HL34625 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Jun 25) 266 (18) 12067-74.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199107
ENTRY DATE: Entered STN: 19910811
Last Updated on STN: 19910811
Entered Medline: 19910724
AB Infusion of tumor necrosis factor (TNF) into tumor-bearing mice led to intravascular clot formation with fibrin deposition in microvessels in the tumor bed in close association with the vessel wall, which could be prevented by active site-blocked **factor** IXa (**IXai**). This observation prompted us to examine the role of the intrinsic system in activation of the coagulation mechanism on TNF-stimulated human endothelial cell monolayers and endothelial-derived matrix during exposure to purified coagulation factors or flowing blood. Treatment of endothelial cells in intact monolayers with TNF induced expression of the procoagulant cofactor tissue factor (TF) in a dose-dependent manner, and after removal of the cells, TF was present in the matrix. TNF-treated endothelial cell monolayers exposed to blood anticoagulated with low molecular weight heparin induced activation of coagulation. Addition of IXai blocked the procoagulant response on TNF-treated endothelial cells, and consistent with this, the presence of **factor IX**/VIIIa enhanced endothelial TF/factor VII(a) factor X activation over a wide range of cytokine concentrations (0-600 pM). When TF-dependent factor X activation on endothelial cells was compared with preparations of subendothelium, the extracellular matrix was 10-20 times more effective. IXai blocked TF/factor VII(a) mediated activated coagulation on matrix, but only at lower concentration of TNF (less than 50 pM). Similarly, enhancement of factor Xa formation on matrix by **factors IX**/VIIIa was most evident at lower TNF concentrations. When anticoagulated whole blood flowing with a shear of 300 s-1 was exposed to matrices from TNF-treated endothelial cells, but not matrices from control cells, fibrinopeptide A (FPA) generation, fibrin deposition, and platelet aggregate formation were observed. FPA generation could be prevented by a blocking antibody to TF and by active site-blocked factor Xa (Xai) over a wide range of TNF concentrations (0-600 pM), whereas IXai only blocked FPA generation at lower TNF concentrations (less than 50 pM). Activation of coagulation on

matrix from TNF-stimulated endothelial cells was dependent on the presence of platelets, indicating the important role of platelets in propagating the reactions leading to fibrin formation. These observations demonstrate the potential of cytokine-stimulated endothelium and their matrix to activate coagulation and suggest the importance of the intrinsic system in factor Xa formation on cellular surfaces.

L4 ANSWER 6 OF 6 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 92042769 MEDLINE
DOCUMENT NUMBER: 92042769 PubMed ID: 1939660
TITLE: Active site-blocked factor IXa prevents intravascular thrombus formation in the coronary vasculature without inhibiting extravascular coagulation in a canine thrombosis model.
AUTHOR: Benedict C R; Ryan J; Wolitzky B; Ramos R; Gerlach M; Tijburg P; **Stern D**
CORPORATE SOURCE: Department of Internal Medicine, University of Texas Medical School, Houston 77225.
CONTRACT NUMBER: HL-34625 (NHLBI)
HL-42507 (NHLBI)
HL-42833 (NHLBI)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1991 Nov) 88 (5) 1760-5.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19920124
Entered Medline: 19911213

AB To assess the contribution of **Factor IX**/IXa, to intravascular thrombosis, a canine coronary thrombosis model was studied. Thrombus formation was initiated by applying current to a needle in the circumflex coronary artery. When 50% occlusion of the vessel developed, the current was stopped and animals received an intravenous bolus of either saline, bovine glutamyl-glycyl-arginyl-**Factor** IXa (**IXai**), a competitive inhibitor of Factor IXa assembly into the intrinsic Factor X activation complex, bovine **Factor IX** , or heparin. Animals receiving saline or **Factor IX** developed coronary occlusion due to a fibrin/platelet thrombus in 70 +/- 11 min. In contrast, infusion of IXai prevented thrombus formation completely (greater than 180 min) at doses of 460 and 300 micrograms/kg, and partially blocked thrombus formation at 150 micrograms/kg. IXai attenuated the accumulation of 125I-fibrinogen/fibrin at the site of the thrombus by approximately 67% (P less than 0.001) and resulted in approximately 26% decrease in serotonin release from platelets in coronary sinus (P less than 0.05). Hemostatic variables in animals receiving IXai, remained within normal limits. Animals given heparin in a concentration sufficient to prevent occlusive thrombosis had markedly increased bleeding, whereas heparin levels that maintained extravascular hemostasis did not prevent intracoronary thrombosis. This suggests that **Factor IX**/IXa can contribute to thrombus formation, and that inhibition of IXa participation in the clotting mechanism blocks intravascular thrombosis without impairing extravascular hemostasis.

=> dis his

(FILE 'HOME' ENTERED AT 12:00:48 ON 06 APR 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:01:09 ON 06 APR 2002
L1 12014 S PINSKY D?/AU OR STERN D?/AU OR SCHMIDT A?/AU OR ROSE E?/AU OR
L2 99 S L1 AND (FACTOR (1N) IX)
L3 13 S L2 (P) (FACTOR (1N) IXAI)
L4 6 DUP REM L3 (7 DUPLICATES REMOVED)

=> s (factor (1N) IXa)
L5 2304 (FACTOR (1N) IXA)

=> s l5 (P) (inhibit? or inactivat? or mutein? or mutate? or alter?)
L6 1183 L5 (P) (INHIBIT? OR INACTIVAT? OR MUTEIN? OR MUTATE? OR ALTER?)

=> s l6 (P) administ?
L7 60 L6 (P) ADMINIST?

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 21 DUP REM L7 (39 DUPLICATES REMOVED)

=> dis l8 1-21 ibib abs

L8 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:828920 CAPLUS
DOCUMENT NUMBER: 135:352799
TITLE: Methods using factor IXa compounds for treating an ischemic disorder and improving stroke outcome
INVENTOR(S): Pinsky, David J.; Stern, David; Schmidt, Ann Marie; Rose, Eric; Solomon, Robert A.
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA
SOURCE: U.S., 56 pp., Cont.-in-part of WO1997US 17,229.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6315995	B1	20011113	US 1998-53871	19980401
WO 9813058	A1	19980402	WO 1997-US17229	19970925

W: AU, CA, JP, MX, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

WO 9949880	A1	19991007	WO 1999-US7175	19990401

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,

MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9934621	A1	19991018	AU 1999-34621	19990401	
EP 1067953	A1	20010117	EP 1999-916266	19990401	

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.:	US 1996-721447	B2 19960927
	WO 1997-US17229	A2 19970925
	US 1998-53871	A2 19980401
	WO 1999-US7175	W 19990401

AB A method for treating an ischemic disorder in a subject comprises **administering** a pharmaceutically acceptable **Factor IXa** compd. in a sufficient amt. over a sufficient period so as to treat the ischemic disorder. The invention further provides a method for treating an ischemic disorder in a subject which comprises **administering** a pharmaceutically acceptable form of **inactivated Factor IXa** in a sufficient amt. over a sufficient period to **inhibit** coagulation so as to treat the ischemic disorder.

REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 21 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001558816 MEDLINE
DOCUMENT NUMBER: 21201952 PubMed ID: 11307818
TITLE: Inhibition of arterial thrombosis by a soluble tissue factor mutant and active site-blocked factors IXa and Xa in the guinea pig.
AUTHOR: Himber J; Refino C J; Burcklen L; Roux S; Kirchhofer D
CORPORATE SOURCE: Preclinical Research Department, F. Hoffman-La Roche Ltd, Basel, Switzerland.. jacques.himber@roche.com
SOURCE: THROMBOSIS AND HAEMOSTASIS, (2001 Mar) 85 (3) 475-81. Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: Germany: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011022
Last Updated on STN: 20011022
Entered Medline: 20011018

AB The substrate recognition region of tissue factor contains two residues, Lys165 and Lys166, which are important for macromolecular substrate activation by the tissue factor:factor VIIa complex. Replacement of these two residues with alanine in a soluble version of human tissue factor resulted in a mutant, hTFAA, which can bind factor VIIa but forms an enzymatically inactive complex. We found that hTFAA **inhibits** the activity of guinea pig factor VIIa, allowing us to evaluate hTFAA's effects on thrombosis and hemostasis in a guinea pig model of recurrent arterial thrombosis. In addition to heparin, the effects of hTFAA were compared to active site **inhibited factor IXa** (F.IXai) and factor Xa (F.Xai). We found that hTFAA, F.IXai and F.Xai were potent antithrombotics and may possess a decreased risk of hemorrhage when compared to unfractionated heparin. When **administered** at a dose that **inhibited** thrombosis by about 90%, hTFAA neither affected cuticle bleeding nor the activated partial thromboplastin time, and had only a modest effect on the prothrombin time. At equi-efficacious doses, F.IXai, F.Xai and heparin prolonged bleeding times by 20% ($p > 0.5$), 50% ($p < 0.05$) and 100% ($p < 0.01$), respectively. In summary, our study demonstrates that, unlike heparin, specific **inhibitors** of **factors** VIIa, **IXa** and Xa can produce antithrombotic effects without or with only minimally disturbing normal hemostasis. The results further suggest that factor VIIa and **factor IXa** are especially promising targets for antithrombotic drug development.

L8 ANSWER 3 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:198784 BIOSIS
DOCUMENT NUMBER: PREV200200198784
TITLE: Monitoring of high dosage of low-molecular-weight heparins: Implications in the treatment and interventional indications.
AUTHOR(S): Fareed, Jawed (1); Hoppensteadt, D. A. (1); Iqbal, O. (1); Walenga, J. M. (1); Ahmad, S. (1); Mayuga, M. (1); Fareed, D. (1); Messmore, H. L. (1)
CORPORATE SOURCE: (1) Pathology, Loyola University of Chicago, Maywood, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 272a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The low molecular weight heparins (LMWHs) are now widely used for the treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE) in both the subcutaneous (s.c.) and intravenous (i.v.) regimens. In the s.c. studies, up to 250 U/kg (simeq3 mg/kg) and in the i.v. studies, up to 100 U/kg (apprx1 mg/kg) dosages are used. These dosages can result in peak circulating concentrations of up to 3.0 U/ml. In several interventional cardiological and other surgical indications, 100 U/kg i.v. bolus of a LMWH with either continuous infusion or additional boli to maintain the activated clotting time (ACT) in the range of 190-210 sec corresponding to concentrations of up to 2.5 U/ml results in an activated partial thromboplastin time (aPTT) increase to 160-190 sec. At this dosing, marked differences in the level of anticoagulation are noted among different LMWHs. These differences are amplified when the LMWHs are **administered** with adjunct drugs such a glycoprotein (GP) IIb/IIIa **inhibitors**. The ACT measurement has been found to correlate with the global anticoagulant efficacy and bleeding. Thus, a recommendation for the optimal range for the ACT and or aPTT for this indication is warranted. While the amidolytic anti-Xa (AXa) may be useful in the monitoring of the pharmacokinetics of these agents the method is not reliable for the monitoring of the global anticoagulant effects. The AXa assays do not measure the global anticoagulant effects of LMWHs, which not only involve the AXa, AIIa, thrombin generation **inhibition** effects and the contribution of the endogenously released mediators, such as the tissue factor pathway **inhibitor** (TFPI). Collectively, these effects influence the global anticoagulant effects of LMWHs, which require monitoring. The AXa methods also depend on the assay design and the type of factor Xa used. Methods requiring the direct activation of

plasmatic factor X to Xa do not compare well with amidolytic methods, which utilize the preformed factor Xa. Activators such as Russells Viper Venom (RVV), activation complex comprising of **factors** VIIIc, **IXa**-PL result in factor Xa with different Km values, provided markedly different results. The AXa assay methods carried out on whole blood (WB) are strongly influenced by matrix and provide highly variable results. In several studies where heparin and various LMWHs were given at 1 mg/kg (n=1,500) for interventional and treatment indications, ACT, aPTT, AXa, AIIa and Heptest times were measured. In addition, thrombin-antithrombin complex (TAT), F1.2, thrombin activatable fibrinolytic **inhibitor** (TAFI) and thrombin generation assays were performed. The aPTT, ACT and Heptest correlated well (r=>0.7) with the thrombogenic measures), whereas the other tests (AXa, AIIa) showed a poor correlation (r<0.5). Thus, at the present time, the high dosage i.v. LMWHs can be best monitored by using the available WB ACT methods. In addition, point-of-care testing to measure the global anticoagulant effect can be carried out using a reliable activated partial thromboplastin time (aPTT) method on whole blood. These results suggest that high dosage of LMWHs is best measured by the global anticoagulant effects, which provide more clinically relevant monitoring.

L8 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 2001:320878 CAPLUS
DOCUMENT NUMBER: 135:220453
TITLE: Emerging anticoagulant and thrombolytic drugs
AUTHOR(S): Iqbal, Omer; Aziz, Salim; Hoppensteadt, Debra A.; Ahmad, Sarfraz; Walenga, Jeanine M.; Bakhos, Mamdouh; Fareed, Jawed
CORPORATE SOURCE: Medical Center, Loyola University Chicago, Maywood, IL, 60153, USA
SOURCE: Emerging Drugs (2001), 6(1), 111-135
CODEN: EMDRFV; ISSN: 1361-9195
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 147 refs. Since its discovery, heparin has been used intensely as an anticoagulant for several medical and surgical indications. However, efforts are in progress to replace heparin because of its serious complications, such as intraoperative and postoperative bleeding, osteoporosis, alopecia, heparin resistance, heparin rebound, heparin-induced thrombocytopenia (HIT) and thrombosis syndrome (HITTS), and other disadvantages. Significant developments in the field of new anticoagulants have resulted in the evaluation and introduction of low mol. wt. heparins (LMWHs) and heparinoids, hirudin, ancrod, synthetic peptides and peptidomimetics. However, despite significant progress in the development of these new anticoagulants, a better or an ideal anticoagulant for cardiovascular patients is not yet available and heparin still continues to amaze both basic scientists and the clinicians. To minimise the adverse effects of heparin, newer approaches to optimize its use in combination with the new anticoagulants may provide better clin. outcome. In our experience, the off-label use of argatroban at a dose of 300 .mu.g/kg iv. bolus followed by 10 .mu.g/kg/min infusion in combination with aggrastat (a glycoprotein [GP] IIb/IIIa **inhibitor**) at a dose of 10 .mu.g/kg iv. bolus followed by an infusion of 0.15 .mu.g/kg/min in patients with HIT undergoing percutaneous coronary interventions resulted in elevation of celite activated clotting time (ACT) to 300 s followed by a gradual decline and the ACT remained above 200 s even after 200 min of drug **administration**. A bewildering array of newer anticoagulants now exist, such as LMWHs and heparinoids, indirect or direct thrombin **inhibitors**, oral thrombin **inhibitors**, such as melagatran (AstraZeneca) and HC-977 (Mitsubishi Pharmaceuticals), **Factor IXa inhibitors**, indirect or direct Factor Xa **inhibitors**, Factor VIIa/tissue factor (TF) pathway **inhibitor**, newer antiplatelet agents, such as GPIIb/IIIa **inhibitors**, fibrin specific thrombolytic agent, such as tenecteplase and modulation of the endogenous fibrinolytic activity by thrombin activatable fibrinolytic **inhibitor** (TAFI), Factor XIIIa **inhibitors** and PAI-1 **inhibitors**. The quest for newer anticoagulant, antiplatelet and fibrinolytic agents will continue until ideal agents are found.
REFERENCE COUNT: 147 THERE ARE 147 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 21 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001156364 MEDLINE
DOCUMENT NUMBER: 21084088 PubMed ID: 11215377
TITLE: New anticoagulants.
AUTHOR: Kawasaki T; Hirayama F
CORPORATE SOURCE: Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, Ibaraki 305-8585, Japan.. kawasat@yamanouchi.co.jp
SOURCE: NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (2000 Nov) 116 (5) 275-82. Ref: 47
Journal code: F2X; 0420550. ISSN: 0015-5691.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322
AB The quest to develop new antithrombotic agents has been stimulated by clinical needs and by advances in biotechnology that have made it possible to produce drugs that target specific steps in thrombogenesis. Established anticoagulants such as unfractionated heparin and the coumarins are effective, but have two major limitations: narrow therapeutic windows and highly unpredictable dose-response relationships. Consequently, these drugs often cause complications such as serious bleeding that require close monitoring of their use by laboratory tests to balance safety and effect. These limitations provided the impetus for the development of new anticoagulants that **inactivate** thrombin, factor Xa, **factor IXa** or the factor VIIa/tissue factor complex. Similarly, agents that enhance the protein C anticoagulant pathway have also been developed. Of these, direct thrombin **inhibitors**, soluble thrombomodulin, protein C, and activated protein C have been evaluated clinically for parenteral **administration**. However, there is enormous interest in the development of safer and more effective oral anticoagulants. In the future, such orally active direct **inhibitors** of thrombin and factor Xa, if they can be given safely

without the need for laboratory monitoring, may replace the coumarins for the long-term treatment of thromboembolic disorders. To achieve these goals, these compounds need high, consistent oral bioavailability.

L8 ANSWER 6 OF 21 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001382637 MEDLINE
DOCUMENT NUMBER: 21150141 PubMed ID: 11251339
TITLE: Does inflammation contribute to thrombotic events?.
AUTHOR: Esmon C T
CORPORATE SOURCE: Oklahoma Medical Research Foundation, Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Okla., USA.. Charles-Esmon@omrf.ouhsc.edu
SOURCE: HAEMOSTASIS, (2000) 30 Suppl 2 34-40. Ref: 35
Journal code: FYG; 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB Recent studies have focused on a myriad of mechanisms by which inflammation can potentiate blood clotting. Inflammatory mediators like endotoxin and tissue necrosis factor (TNF)-alpha can cause the expression of tissue factor on monocytes and, possibly, endothelium, thereby initiating the coagulation cascade. Activation of the complement system can lead to exposure of membrane surfaces capable of amplifying the initial tissue factor stimulus by facilitating the assembly of the factor VIIIa-**factor IXa** and the factor Xa-factor Va complexes. Inflammatory mediators, particularly interleukin-6, can also increase the levels of fibrinogen, an acute-phase reactant. In addition, the inflammatory mediators can elevate the levels of plasminogen activator **inhibitor**, thus suppressing the fibrinolytic system. These studies alone, however, do not prove that inflammation can trigger clinically relevant thrombus formation in vivo. For instance, TNF-alpha has been studied in cancer patients as a potential cure for cancer, and even though these patients are hypercoaguable, thrombosis was not commonly observed as a side effect of the near-lethal doses of TNF-alpha that were **administered**. Based on primate studies, inflammatory mediators like TNF-alpha can promote clot deposition effectively only if there is reduced flow and **inhibition** of the natural anticoagulant pathways. The requirement for multiple simultaneous injurious events probably explains why inflammation alone is not observed as a major cause of thrombosis. Copyright 2001 S. Karger AG, Basel

L8 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 1999:794322 CAPLUS
DOCUMENT NUMBER: 132:18789
TITLE: Compositions and methods using an oxidized/reduced low-molecular-weight heparin compound for inhibiting thrombogenesis
INVENTOR(S): Hirsh, Jack; Weitz, Jeffrey I.
PATENT ASSIGNEE(S): Hamilton Civic Hospitals Research Development Inc., Can.
SOURCE: U.S., 48 pp., Cont.-in-part of U.S. 5,763,427.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6001820	A	19991214	US 1997-870528	19970606
US 5744457	A	19980428	US 1995-540324	19951006
AU 9651400	A1	19961016	AU 1996-51400	19960329
US 5763427	A	19980609	US 1996-624327	19960329
JP 11506420	T2	19990608	JP 1996-528734	19960329
NO 9704500	A	19971128	NO 1997-4500	19970929

PRIORITY APPLN. INFO.: US 1995-412332 19950331
US 1995-540324 19951006
US 1996-624327 19960329
WO 1996-CA190 19960329
OTHER SOURCE(S): MARPAT 132:18789

AB Compns. and methods are provided for the treatment of cardiovascular diseases. More particularly, the invention relates to modifying thrombus formation by **administering** an agent which, inter alia, is capable of (1) selectively **inactivating** thrombin which is bound either to fibrin in a clot or to some other surface, but which has only minimal **inhibitory** activity against free thrombin, i.e., fluid-phase thrombin; (2) **inhibiting** the assembly of the intrinsic tenase complex, thereby **inhibiting** the activation of Factor X by **Factor IXa**; and (3) **inhibiting** the activation of Factor IX by Factor XIa. The compns. and methods of the present invention are particularly useful for preventing thrombosis in the circuit of cardiac bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from thrombus-related cardiovascular conditions, such as unstable angina, acute myocardial infarction (heart attack), cerebrovascular accidents (stroke), pulmonary embolism, deep vein thrombosis, arterial thrombosis, etc. The invention uses a polyanionic carbohydrate, esp. an oxidized/reduced low-mol.-wt. heparin compd. (prepn. described).
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:640718 CAPLUS
DOCUMENT NUMBER: 131:267054
TITLE: Methods using a factor IXa compound for treating an ischemic disorder and improving stroke outcome
INVENTOR(S): Pinsky, David J.; Stern, David; Schmidt, Ann Marie; Rose, Eric; Solomon, Robert A.
PATENT ASSIGNEE(S): The Trustees of Columbia University In the City of New York, USA
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9949880	A1	19991007	WO 1999-US7175	19990401
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6315995	B1	20011113	US 1998-53871	19980401
AU 9934621	A1	19991018	AU 1999-34621	19990401
EP 1067953	A1	20010117	EP 1999-916266	19990401
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-53871 A2 19980401
US 1996-721447 B2 19960927
WO 1997-US17229 A2 19970925
WO 1999-US7175 W 19990401

AB A method is provided for treating an ischemic disorder in a subject which comprises **administering** to the subject a pharmaceutically acceptable **factor IXa** compd. in a sufficient amt. over a sufficient period to treat the ischemic disorder. The invention further provides a method for treating an ischemic disorder in a subject which comprises **administering** to the subject a pharmaceutically acceptable form of **inactivated Factor IXa** in a sufficient amt. over a sufficient period of time to **inhibit** coagulation so as to treat the ischemic disorder.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 21 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999422977 MEDLINE
DOCUMENT NUMBER: 99422977 PubMed ID: 10494786
TITLE: A human antibody that binds to the gamma-carboxyglutamic acid domain of factor IX is a potent antithrombotic in vivo.
AUTHOR: Refino C J; Himber J; Burcklen L; Moran P; Peek M; Suggett S; Devaux B; Kirchhofer D
CORPORATE SOURCE: Genentech Inc., Cardiovascular Research Department, South San Francisco, CA 94080, USA.. ken@gene.com
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1999 Sep) 82 (3) 1188-95. Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991122

AB 10C12, a human antibody F(ab')2, which specifically binds to the Gla domain of factor IX, interfered with all known coagulation processes that involve **factor** IX/**IXa**. These include the function of the intrinsic Xase complex and the activation of zymogen factor IX by factor XIa and by the tissue factor:factor VIIa complex. Furthermore, 10C12 potently **inhibited** activated partial thromboplastin clotting times (APTT) in plasma of guinea pig and rat, thus enabling in-vivo evaluation. In guinea pigs, a bolus **administration** of 10C12 (10 microg/kg) prevented cyclic flow variations in damaged carotid arteries without affecting coagulation or bleeding parameters. At a 100-fold higher dose, 10C12 had no effect on normal hemostasis as assessed by the cuticle bleeding time. At this dose, 10C12 was also efficacious in a rat arterial thrombosis model, substantially reducing clot weight and duration of vessel occlusion while prolonging ex-vivo APTT only 1.2-fold. The dose of heparin required to produce comparable antithrombotic effects prolonged the APTT by 12-fold and increased the tail bleeding time (TBT) by 8-fold. In contrast, 10C12 had no effect on TBT. However, rat tails showed a tendency for rebleeding which 10C12 exacerbated. In conclusion, the antithrombotic potency of the 10C12 antibody in two species provides evidence for an important role of F.IX, and its Gla domain in particular, during thrombogenesis under arterial flow conditions. The relative safety at effective doses of this fully human antibody suggests that it may have therapeutic value for treatment of thrombotic disorders.

L8 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 8
ACCESSION NUMBER: 1999:601274 CAPLUS
DOCUMENT NUMBER: 131:298639
TITLE: Accumulation of antibody-target complexes and the pharmacodynamics of clotting after single intravenous administration of humanized anti-Factor IX monoclonal antibody to rats
AUTHOR(S): Davis, Charles B.; Tobia, LeeAnn P.; Kwok, Deborah C.; Oishi, Christine M.; Kheterpal, Neil; Hepburn, Timothy W.; Benincosa, Lisa J.; Chow, Fung-Sing; Jusko, William J.
CORPORATE SOURCE: Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Drug Delivery (1999), 6(3), 171-179
CODEN: DDELEB; ISSN: 1071-7544
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English

AB SB-249417, a humanized monoclonal antibody (Mab) specific for the Gla domain of Factor IX, **inhibits** activation of this zymogen and blocks the activity of **Factor IXa** on **Factor** X, the subsequent enzyme in the clotting cascade. In the present study, the pharmacokinetics and pharmacodynamics of SB-249417 were investigated in male Sprague-Dawley rats after IV **administration** of single doses of 10, 50, or 250 mg/kg. Blood samples were collected for up to six weeks to assess total plasma Mab concn. and activated partial thromboplastin time (aPTT). A PK/PD model was developed using an empirical relationship between aPTT and the concn. of free Factor IX (**inhibitory** Emax model). The model assumed natural synthesis and degrdn. of the endogenous zymogen that was interrupted by the complexation of Factor IX with the antibody. Following antibody **administration** , aPTT values increased .apprx.5-fold above baseline at the earliest sampling time in all dose groups. Higher doses led to a longer duration of prolonged clotting time. Ests. of model parameters yielded a Kd for

antibody-antigen interaction (38 nM) that was similar to the in vitro value. The estd. degrdn. half-life of Factor IX (8 h) was consistent with historical ests. The PK/PD model predicted that the max. concn. of antibody-Factor IX complex (Cmax) and the time to Cmax (Tmax) would increase with increasing dose. The extent of accumulation, up to .apprx.10-fold greater than the concn. of endogenous Factor IX at baseline, was confirmed by Western Blot anal. of Protein A exts. Complex Tmax was similar to the duration of pharmacol. effect and suggests effects persisted until Factor IX synthesis produced sufficient antigen to sat. the antibody.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 21 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1999358304 MEDLINE
DOCUMENT NUMBER: 99358304 PubMed ID: 10429673
TITLE: Targeted inhibition of intrinsic coagulation limits cerebral injury in stroke without increasing intracerebral hemorrhage.
AUTHOR: Choudhri T F; Hoh B L; Prestigiacomo C J; Huang J; Kim L J; Schmidt A M; Kisiel W; Connolly E S Jr; Pinsky D J
CORPORATE SOURCE: Department of Neurological Surgery, University College of Physicians and Surgeons, New York 10032, USA.
CONTRACT NUMBER: K08 NS02038 (NINDS)
R01 HL55397 (NHLBI)
R01 HL59488 (NHLBI)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1999 Jul 5) 190 (1) 91-9.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 20000303
Entered Medline: 19990824

AB Agents that restore vascular patency in stroke also increase the risk of intracerebral hemorrhage (ICH). As **Factor IXa** is a key intermediary in the intrinsic pathway of coagulation, targeted **inhibition** of **Factor IXa**-dependent coagulation might **inhibit** microvascular thrombosis in stroke without impairing extrinsic hemostatic mechanisms that limit ICH. A competitive **inhibitor** of native **Factor IXa** for assembly into the intrinsic Factor X activation complex, Factor IXai, was prepared by covalent modification of the **Factor IXa** active site. In a modified cephalin clotting time assay, in vivo **administration** of Factor IXai caused a dose-dependent increase in time to clot formation (3.6-fold increase at the 300 micrograms/kg dose compared with vehicle-treated control animals, $P < 0.05$). Mice given Factor IXai and subjected to middle cerebral artery occlusion and reperfusion demonstrated reduced microvascular fibrin accumulation by immunoblotting and immunostaining, reduced 111In-labeled platelet deposition (42% decrease, $P < 0.05$), increased cerebral perfusion (2.6-fold increase in ipsilateral blood flow by laser doppler, $P < 0.05$), and smaller cerebral infarcts than vehicle-treated controls (70% reduction, $P < 0.05$) based on triphenyl tetrazolium chloride staining of serial cerebral sections. At therapeutically effective doses, Factor IXai was not associated with increased ICH, as opposed to tissue plasminogen activator (tPA) or heparin, both of which significantly increased ICH. Factor IXai was cerebroprotective even when given after the onset of stroke, indicating that microvascular thrombosis continues to evolve (and may be **inhibited**) even after primary occlusion of a major cerebrovascular tributary.

L8 ANSWER 12 OF 21 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998384224 MEDLINE
DOCUMENT NUMBER: 98384224 PubMed ID: 9716589
TITLE: Phosphorothioate oligonucleotides inhibit the intrinsic tenase complex.
AUTHOR: Sheehan J P; Lan H C
CORPORATE SOURCE: University of Texas Health Science Center at San Antonio, Department of Medicine/Hematology, San Antonio, TX, USA.. sheehan@uthscsa.edu
CONTRACT NUMBER: 1 K08 HL 02923 (NHLBI)
SOURCE: BLOOD, (1998 Sep 1) 92 (5) 1617-25.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980910

AB Systemic **administration** of ISIS 2302, a 20-mer antisense phosphorothioate oligonucleotide targeting human intercellular adhesion molecule-1 mRNA, causes prolongation of plasma clotting times in both monkey and human studies. The anticoagulant effects of ISIS 2302 were investigated with both in vitro coagulation assays in human plasma and purified enzyme systems. At high oligonucleotide plasma concentrations (>100 microgram/mL), prolongation of the prothrombin and thrombin times was observed. In a thrombin time assay using purified components, high concentrations of ISIS 2302 **inhibited** thrombin clotting activity both by stimulating **inhibition** by heparin cofactor II and directly competing with fibrinogen for binding to anion binding exosite I. In contrast, low concentrations of ISIS 2302 (<100 microgram/mL) showed a selective, linear prolongation of the activated partial thromboplastin time (PTT). The rate limiting effect of 50 microgram/mL ISIS 2302, which prolonged the PTT to 1.5 times control, was identified by sequential modification of the clotting assay. Delaying addition of oligonucleotide until after contact activation failed to correct prolongation of the PTT. The calcium-dependent steps of the intrinsic pathway were individually assessed by adding sufficient activated coagulation factor to correct the PTT in plasma deficient in that specific factor. Addition of **factor** XIa, **IXa**, VIIIa, or Va failed to correct the PTT in the presence of ISIS 2302. In contrast, 0.2 nmol/L factor Xa corrected prolongation of the PTT in factor X-deficient plasma with or without oligonucleotide present. ISIS 2302 (50 microgram/mL) did not prolong a modified Russel viper venom time, suggesting no significant **inhibition** of prothrombinase. Thus, 50 microgram/mL ISIS 2302 prolonged the PTT by selectively **inhibiting** intrinsic tenase activity. ISIS 2302 showed partial **inhibition** of intrinsic

tenase activity (to approximately 35% of control) at clinically relevant oligonucleotide concentrations in a chromogenic assay. This activity was oligonucleotide sequence-independent but required the phosphorothioate backbone, suggesting that **inhibition** of intrinsic tenase is a general property of this class of oligonucleotides. These results are relevant to both the therapeutic use of phosphorothioate oligonucleotides and the potential design of **inhibitors** of the intrinsic tenase complex, a novel target for anticoagulation.

L8 ANSWER 13 OF 21 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998266125 MEDLINE
DOCUMENT NUMBER: 98266125 PubMed ID: 9605089
TITLE: Heparinless cardiopulmonary bypass with active-site blocked factor IXa: a preliminary study on the dog.
AUTHOR: Spanier T B; Oz M C; Minanov O P; Simantov R; Kisiel W; Stern D M; Rose E A; Schmidt A M
CORPORATE SOURCE: Department of Surgery, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA.
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1998 May) 115 (5) 1179-88.
Journal code: K9J; 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980616

AB OBJECTIVE: Cardiopulmonary bypass is a potent stimulus for activation of procoagulant pathways. Heparin, the traditional antithrombotic agent, however, is often associated with increased perioperative blood loss because of its multiple sites of action in the coagulation cascade and its antiplatelet and profibrinolytic effects. Furthermore, heparin-mediated immunologic reactions (that is, heparin-induced thrombocytopenia) may contraindicate its use. Cardiopulmonary bypass with a selective **factor IXa inhibitor** was tested to see whether it could effectively limit bypass circuit/intravascular space thrombosis while decreasing extravascular bleeding, thereby providing an **alternative** anticoagulant strategy when heparin may not be safely **administered**. METHODS: Active site-blocked **factor IXa**, a competitive **inhibitor** of the assembly of **factor IXa** into the factor X activation complex, was prepared by modification of the enzyme's active site by the use of dansyl glutamic acid-glycine-arginine-chlormethylketone. Twenty mongrel dogs (five were given standard heparin/protamine; 15 were given activated site-blocked **factor IXa** doses ranging from 300 to 600 microg/kg) underwent 1 hour of hypothermic cardiopulmonary bypass, and blood loss was monitored for 3 hours after the procedure. RESULTS: Use of activated site-blocked **factor IXa** as an anticoagulant in cardiopulmonary bypass limited fibrin deposition within the extracorporeal circuit as assessed by scanning electron microscopy, comparable with the antithrombotic effect seen with heparin. In contrast to heparin, effective antithrombotic doses of activated site-blocked **factor IXa** significantly diminished blood loss in the thoracic cavity and in an abdominal incisional bleeding model. CONCLUSION: These initial studies on the dog suggest that **administration** of activated site-blocked **factor IXa** may be an effective **alternative** anticoagulant strategy in cardiopulmonary bypass when heparin is contraindicated, affording **inhibition** of intravascular/extracorporeal circuit thrombosis with enhanced hemostasis in the surgical wound.

L8 ANSWER 14 OF 21 CAPLUS
ACCESSION NUMBER: 1996:254276 CAPLUS
DOCUMENT NUMBER: 124:340904
TITLE: Methods and bifunctional ligands for specific tumor inhibition by blood coagulation in tumor vasculature
INVENTOR(S): Thorpe, Philip E.; Edgington, Thomas S.
PATENT ASSIGNEE(S): Univ. of Texas System, USA; Scripps Res. Inst.
SOURCE: PCT Int. Appl., 325 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9601653	A1	19960125	WO 1995-US7439	19950607
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2194369	AA	19960125	CA 1995-2194369	19950607
AU 9528249	A1	19960209	AU 1995-28249	19950607
AU 702250	B2	19990218		
EP 771216	A1	19970507	EP 1995-923817	19950607
EP 771216	B1	20010117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1162267	A	19971015	CN 1995-194801	19950607
BR 9508402	A	19971021	BR 1995-8402	19950607
HU 76970	A2	19980128	HU 1997-84	19950607
HU 220347	B	20011228		
JP 10505327	T2	19980526	JP 1995-504299	19950607
AT 198712	E	20010215	AT 1995-923817	19950607
ES 2153483	T3	20010301	ES 1995-923817	19950607

PRIORITY APPLN. INFO.: US 1994-273567 A 19940711
WO 1995-US7439 W 19950607

AB Bispecific binding ligands are provided which bind through a 1st binding region to a disease-related target cell, e.g. a tumor cell or tumor vasculature; the 2nd region has coagulation-promoting activity or is a binding region for a coagulation factor. Since tumor vasculature is prothrombotic and is predisposed towards coagulation, these targeted coagulants selectively induce blood coagulation in vessels supplying the tumor and cause death of tumor cells. The bispecific binding ligand may be a bispecific (monoclonal) antibody, or the 2 ligands may be connected by a (selectively cleavable) covalent bond, a chem. linking agent, an avidin-biotin linkage, etc. The target of the 1st binding region may be a

cytokine-inducible component, and cytokine may be release in response to a leukocyte-activating antibody; this may be a bispecific antibody which crosslinks activated leukocytes with tumor cells. **Alternatively**, the target of the 1st binding region may be a component (e.g. E- or P-selectin) which is inducible by thrombin, where thrombin prodn. is induced by **administration** of a bispecific antibody which binds to a tumor cell and to tissue factor, prothrombin, factor VII/VIIa, **factor** IX/**IXa**, etc. Thus, a coaguligand (bispecific antibody capable of targeting a coagulant to a tumor site) was prepd. by chem. coupling an Fab' fragment from monoclonal antibody B21-2 (which reacts with I-Ad antigen expressed on A20 B-cell lymphoma cells and on the vasculature of C1300 transfectant mouse tumors) with an Fab' fragment from monoclonal antibody 10H10 (which reacts with human tissue factor). Incubation of A20 cells with this bispecific antibody and recombinant human truncated tissue factor resulted in tethering of tissue factor to the cells; plasma added to the A20 cell-tissue factor complex coagulated rapidly. Kits comprising the bifunctional ligand, a 2nd ligand, and optionally a drug for conjunctive therapy are described.

L8 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:702042 CAPLUS
DOCUMENT NUMBER: 126:31658
TITLE: Peptide boronic acid inhibitors of trypsin-like enzymes
INVENTOR(S): Claeson, Goran; Philipp, Manfred H. W.; Metternich, Rainer
PATENT ASSIGNEE(S): Thrombosis Research Institute, UK
SOURCE: U.S., 13 pp. Cont. of U.S. Ser. No. 998, 632, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5574014	A	19961112	US 1994-240606	19940510
US 5856306	A	19990105	US 1995-459177	19950602
US 6114308	A	20000905	US 1998-79243	19980514
US 6313096	B1	20011106	US 2000-543675	20000407

PRIORITY APPLN. INFO.:
US 1988-181511 B2 19880428
GB 1989-2304 A 19890202
US 1989-406663 B1 19890913
US 1991-680496 B1 19910404
US 1991-795219 B1 19911120
US 1992-998632 B1 19921230
US 1994-240606 A1 19940510
US 1995-459177 A1 19950602
US 1998-79243 A1 19980514

OTHER SOURCE(S): MARPAT 126:31658
AB Peptide boronic acids XYNHCH[(CH2)3OR]BQ1Q2 (I; X = H, N-protecting group; Y = Phe-Pro; Q1Q2 = diol residue; R = C1-4 alkyl) are **inhibitors** of trypsinlike enzymes (including trypsin, thrombin, factor Xa, **factor IXa**, **factor** VIIa, factor XIIa, plasmin, acrosin, complement proteases, kallikrein, urokinase, and tissue plasminogen activator), and may be **administered** orally or parenterally as antithrombotics. They have a rapid onset of activity and low toxicity. Thus, benzyloxycarbonyl-D-phenylalanine p-nitrophenyl ester was condensed with proline, converted to the N-hydroxysuccinimidyl ester, coupled with the (+)-pinanediol ester of (TMS)2NCH[(CH2)3Br]B(OH)2, and reacted with guanidine-HCl and MeONa in MeOH to produce I [X = PhCH2O2C; Y = D-Phe-L-Pro; R = OMe; Q1Q2 = (+)-pinanediyl].

L8 ANSWER 16 OF 21 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 97059856 MEDLINE
DOCUMENT NUMBER: 97059856 PubMed ID: 8904177
TITLE: Determinants of coagulation activation in humans.
AUTHOR: Bauer K A; Eichinger S; Mannucci P M; Rosenberg R D
CORPORATE SOURCE: Hematology-Oncology Section, Department of Medicine, Brockton-West Roxbury Department of Veterans Affairs Medical Center, Massachusetts 02132, USA.
CONTRACT NUMBER: PO1 HL 33014 (NHLBI)
SOURCE: HAEMOSTASIS, (1996) 26 Suppl 1 72-5. Ref: 11
Journal code: FYG; 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19990129
Entered Medline: 19970219
AB To evaluate the mechanism responsible for the generation of factor VIIa in vivo, we measured the levels of this enzyme after **administering** purified factor IX concentrates to patients with hemophilia B. Their factor VIIa levels were initially very low and gradually increased to normal, but there were no significant changes in the generation of factor Xa or thrombin. The **administration** of 10 mu g/kg body weight of recombinant factor VIIa to patients with factor VII deficiency increased the circulating levels 35-fold, but this only resulted in normalization of the activation of factor IX and factor X. Our data indicate that **factor IXa** is primarily responsible for the basal levels of free factor VIIa in vivo, and that changes in free factor VIIa in the blood do not necessarily lead to **alterations** in factor X activation.

L8 ANSWER 17 OF 21 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 96017235 MEDLINE
DOCUMENT NUMBER: 96017235 PubMed ID: 7579395
TITLE: Determinants of plasma factor VIIa levels in humans.
AUTHOR: Eichinger S; Mannucci P M; Tradati F; Arbini A A; Rosenberg R D; Bauer K A
CORPORATE SOURCE: Department of Medicine, Brockton-West Roxbury Department of Veterans Affairs Medical Center, Boston, MA, USA.
CONTRACT NUMBER: PO1 HL 33014 (NHLBI)
SOURCE: BLOOD, (1995 Oct 15) 86 (8) 3021-5.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19990129
Entered Medline: 19951129

AB Several enzymes can activate factor VII in vitro, but the protease responsible for generating factor VIIa in vivo has not been determined. Using recombinant tissue factor that has undergone a COOH-terminal truncation, a sensitive functional assay has been established for measuring plasma factor VIIa levels. To evaluate the mechanism responsible for the generation of factor VIIa in vivo, we measured the levels of this enzyme after **administering** purified concentrates of factor IX and factor VIII to patients with severe deficiencies of these clotting factors. In patients with hemophilia B, factor VIIa levels were initially reduced to 0.5 +/- 0.1 ng/mL and gradually increased to normal after infusing 100 U/kg of body weight (BW) of factor IX. Despite these increases, there were no significant changes in the generation of factor Xa or thrombin. In patients with hemophilia A, only a slight reduction in factor VIIa levels (2.5 +/- 1.3 ng/mL) was observed as compared with controls (3.3 +/- 1.1 ng/mL) and no significant changes were observed after factor VIII levels were normalized. The **administration** of recombinant factor VIIa (10 micrograms/kg BW) to patients with factor VII deficiency increased the mean circulating level of the enzyme to 118 ng/mL, but this only resulted in normalization of the levels of the activation peptides of factor IX and factor X. The above data indicate that **factor IXa** is primarily responsible for the basal levels of free factor VIIa generated in vivo (ie, in the absence of thrombosis or provocative stimuli) and that changes in the plasma concentrations of free factor VIIa in the blood do not necessarily lead to **alterations** in the extent of factor X activation.

L8 ANSWER 18 OF 21 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 95389409 MEDLINE
DOCUMENT NUMBER: 95389409 PubMed ID: 7660358
TITLE: Comparative study on the use of anticoagulants heparin and recombinant hirudin in a rabbit traumatic anastomosis model.
AUTHOR: Fu K; Izquierdo R; Walenga J M; Fareed J
CORPORATE SOURCE: Department of Surgery, Loyola University Chicago Stritch School of Medicine, Maywood, IL 60153, USA.
SOURCE: THROMBOSIS RESEARCH, (1995 Jun 1) 78 (5) 421-8.
Journal code: VRN; 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951013
Last Updated on STN: 19951013
Entered Medline: 19951002

AB Antithrombotic drugs, such as heparin, have been used in the clinics for a long time. Heparin acts by binding with antithrombin III to form a complex thereby enhancing the activity of antithrombin III to **inactivate** coagulation **factors** IIa, **IXa**, Xa, XIa and XIIa. Hirudin is a new antithrombotic agent and is reported to be much more powerful than heparin on a gravimetric basis. When both are **administered** systemically, one of the common complications seen is bleeding. Some previous studies have shown that local vascular endothelial concentrations of heparin are 30 to 7500 times greater than those found in the circulating blood. In order to avoid such complications, topical **administration** of antithrombotic drugs may be an ideal route of **administration**. The rabbit ear arterial crush-avulsion thrombosis model was used in this study. The animals were divided into five groups: one control group and four treatment groups which received varying concentrations of heparin and hirudin. In the saline control group, the patency rate was 19.23% at 24 hrs and 15.38% at 7 days. A higher patency rate at 7 days was obtained in groups treated with high concentration of heparin and hirudin. ACT, PT and APTT performed on samples drawn one hour after drug **administration** were within the normal range in both the control and the treatment groups. Scanning electron microscopy revealed the different extent of the clots on the injured intimal surfaces of the vessels in different groups. The results indicate that high concentrations of topically **administered** heparin or hirudin minimize the systemic complications and maximize the antithrombotic effects.

L8 ANSWER 19 OF 21 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 88288042 MEDLINE
DOCUMENT NUMBER: 88288042 PubMed ID: 3398774
TITLE: Partial deletion by illegitimate recombination of the factor IX gene in a haemophilia B family with two inhibitor patients.
AUTHOR: Green P M; Bentley D R; Mibashan R S; Giannelli F
CORPORATE SOURCE: Paediatric Research Unit, UMDS, London, England.
SOURCE: MOLECULAR BIOLOGY AND MEDICINE, (1988 Apr) 5 (2) 95-106.
Journal code: MOL; 8403879. ISSN: 0735-1313.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M21002
ENTRY MONTH: 198809
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19990129
Entered Medline: 19880901

AB The **inhibitor** phenotype occurs in six haemophilia B patients in the UK and results from development of antibodies by the patients to **administered** factor IX. We have analysed a partial factor IX gene deletion (London 1) in a family with two **inhibitor** patients. The deletion results in retention of the first five exons which code for the light chain of **factor IXa**, and removal of 23 kb of DNA starting 704 bp 3' of the fifth exon and terminating 10.3 kb 3' of the last exon. The 5' break is at residue -113 of an Alu repeat. No significant homology exists between the 5' and 3' termini, but a 9 bp region of complementarity is found 23 bp and 60 bp from the 5' and 3' terminus, respectively. At the cloned deletion junction a new 16 bp sequence contributes a DraI site that is also found in the genomic DNA of the two patients and a heterozygous relative. The deletion is an example of illegitimate recombination and it is proposed that such deletions occur principally during DNA replication. Loss of the 3' sequences involved in the maturation of mRNA probably results in no factor IX production. Immunological studies show that the index patient's antibodies bind both to epitopes coded by deleted and by non-deleted segments of the gene.

L8 ANSWER 20 OF 21 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 87178912 MEDLINE
DOCUMENT NUMBER: 87178912 PubMed ID: 2436336
TITLE: Evaluation of p-amidinophenyl esters as potential antithrombotic agents.
AUTHOR: Pizzo S V; Turner A D; Porter N A; Gonias S L
CONTRACT NUMBER: HL-17921 (NHLBI)
HL-24066 (NHLBI)
HL-31932 (NHLBI)
SOURCE: THROMBOSIS AND HAEMOSTASIS, (1986 Dec 15) 56 (3) 387-90.
Journal code: VQ7; 7608063. ISSN: 0340-6245.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198705
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 19970203
Entered Medline: 19870506

AB Three p-amidinophenyl esters have been synthesized and characterized as irreversible **inhibitors** of the vitamin-K dependent proteinases; **factors IXa**, Xa and thrombin (Turner et al. [4]).+ In the present report we describe the in vitro and in vivo effects of these agents on standard coagulation tests in vitro and in blood from animals treated with the compounds. At a concentration of 500 microM, the three esters increased the activated partial thromboplastin time (PTT) of pooled human plasma 3 to 5-fold. The prothrombin time increased 1.4 to 3.7-fold under similar conditions. The p-amidinophenyl ester of cinnamic acid (CINN) showed the most pronounced effect on both assays. This ester also is the best **inhibitor** of human **factors IXa** and Xa, while the p-amidinophenyl ester of benzoic acid (BENZ) is a slightly better alpha-thrombin **inhibitor** (4). The effect of these esters on the thrombin clotting time correlated with in vitro kinetic measurements of alpha-thrombin **inhibition** rates. Both BENZ and CINN increased the assay endpoint more than 6-fold. The three esters also were studied using mouse plasma. A comparable effect on the PTT was noted. Intravenous **administration** of 300 microliter of 1 mM CINN as a single bolus in mice caused a 2.3-fold increase in the PTT which remained 1.2-fold normal 2 h later. The BENZ and alpha-methyl-cinnamic acid (MECINN) esters were somewhat less effective as predicted from their in vitro effect on the PTT. This investigation and previous studies indicate that these compounds demonstrate low toxicity at therapeutic levels. It is concluded that the p-amidinophenyl esters may be useful in antithrombotic therapy.

L8 ANSWER 21 OF 21 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 85200265 MEDLINE
DOCUMENT NUMBER: 85200265 PubMed ID: 3995170
TITLE: In vivo studies of the role of factor VII in hemostasis.
AUTHOR: Giles A R; Tinlin S; Brosseau L; Hoogendoorn H
SOURCE: BLOOD, (1985 May) 65 (5) 1197-200.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198506
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850625

AB The effect of both congenital and acquired factor VII deficiency on the cuticle bleeding time (CBT) was evaluated in dogs. The CBT has been previously documented to be a sensitive indicator of factor VIII:C deficiency in hemophilic dogs. Serial CBT determinations were made on normal dogs treated with high-dose warfarin. At 48 hours post-treatment, the CBT was normal, although the factor VII level was less than 1%, whereas the levels of factors II, IX, and X were 44%, 25%, and 17%, respectively. At 120 hours the CBT became abnormal when all vitamin K-dependent clotting factors had dropped to less than 18%. **Administration** of a plasma concentrate of factors II, IX, and X corrected the CBT, despite the factor VII level remaining at less than 1%. Similar studies in a congenitally factor VII-deficient dog (factor VII less than 2%) confirmed that this deficiency state was not associated with an abnormality of the CBT. **Administration** of heparin to both normal and factor VII-deficient animals was associated with prolongation of the CBT, but the heparin dose required in the normal animals was substantially higher than in the factor VII-deficient animals. These data do not suggest that factor VII/VIIa has an exclusive role in generating factor Xa, either directly or indirectly, by way of **factor IXa** generation, in vivo. However, the increase in heparin sensitivity of the factor VII-deficient animals does suggest that factor VII/VIIa may, in some circumstances, present a significant **alternative** pathway of factor X activation, although the activation pathway involved cannot be determined from the studies performed.

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(FILE 'HOME' ENTERED AT 12:00:48 ON 06 APR 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:01:09 ON 06 APR 2002
L1 12014 S PINSKY D?/AU OR STERN D?/AU OR SCHMIDT A?/AU OR ROSE E?/AU OR
L2 99 S L1 AND (FACTOR (1N) IX)
L3 13 S L2 (P) (FACTOR (1N) IXAI)
L4 6 DUP REM L3 (7 DUPLICATES REMOVED)
L5 2304 S (FACTOR (1N) IXA)
L6 1183 S L5 (P) (INHIBIT? OR INACTIVAT? OR MUTEIN? OR MUTATE? OR ALTE
L7 60 S L6 (P) ADMINIST?
L8 21 DUP REM L7 (39 DUPLICATES REMOVED)

=> s l7 (P) (thrombolytic or fibrinolytic)
L9 6 L7 (P) (THROMBOLYTIC OR FIBRINOLYTIC)

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 3 DUP REM L9 (3 DUPLICATES REMOVED)

=> dis l10 1-3 ibib abs

L10 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:198784 BIOSIS

DOCUMENT NUMBER: PREV200200198784
TITLE: Monitoring of high dosage of low-molecular-weight heparins: Implications in the treatment and interventional indications.
AUTHOR(S): Fareed, Jawed (1); Hoppensteadt, D. A. (1); Iqbal, O. (1); Walenga, J. M. (1); Ahmad, S. (1); Mayuga, M. (1); Fareed, D. (1); Messmore, H. L. (1)
CORPORATE SOURCE: (1) Pathology, Loyola University of Chicago, Maywood, IL USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 272a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The low molecular weight heparins (LMWHs) are now widely used for the treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE) in both the subcutaneous (s.c.) and intravenous (i.v.) regimens. In the s.c. studies, up to 250 U/kg (simeq3 mg/kg) and in the i.v. studies, up to 100 U/kg (apprx1 mg/kg) dosages are used. These dosages can result in peak circulating concentrations of up to 3.0 U/ml. In several interventional cardiological and other surgical indications, 100 U/kg i.v. bolus of a LMWH with either continuous infusion or additional boli to maintain the activated clotting time (ACT) in the range of 190-210 sec corresponding to concentrations of up to 2.5 U/ml results in an activated partial thromboplastin time (aPTT) increase to 160-190 sec. At this dosing, marked differences in the level of anticoagulation are noted among different LMWHs. These differences are amplified when the LMWHs are **administered** with adjunct drugs such a glycoprotein (GP) IIb/IIIa **inhibitors**. The ACT measurement has been found to correlate with the global anticoagulant efficacy and bleeding. Thus, a recommendation for the optimal range for the ACT and or aPTT for this indication is warranted. While the amidolytic anti-Xa (AXa) may be useful in the monitoring of the pharmacokinetics of these agents the method is not reliable for the monitoring of the global anticoagulant effects. The AXa assays do not measure the global anticoagulant effects of LMWHs, which not only involve the AXa, AIIa, thrombin generation **inhibition** effects and the contribution of the endogenously released mediators, such as the tissue factor pathway **inhibitor** (TFPI). Collectively, these effects influence the global anticoagulant effects of LMWHs, which require monitoring. The AXa methods also depend on the assay design and the type of factor Xa used. Methods requiring the direct activation of plasmatic factor X to Xa do not compare well with amidolytic methods, which utilize the preformed factor Xa. Activators such as Russells Viper Venom (RVV), activation complex comprising of **factors** VIIIc, **IXa**-PL result in factor Xa with different Km values, provided markedly different results. The AXa assay methods carried out on whole blood (WB) are strongly influenced by matrix and provide highly variable results. In several studies where heparin and various LMWHs were given at 1 mg/kg (n=1,500) for interventional and treatment indications, ACT, aPTT, AXa, AIIa and Heptest times were measured. In addition, thrombin-antithrombin complex (TAT), F1.2, thrombin activatable **fibrinolytic inhibitor** (TAFI) and thrombin generation assays were performed. The aPTT, ACT and Heptest correlated well (r=>0.7) with the thrombogenic measures), whereas the other tests (AXa, AIIa) showed a poor correlation (r<0.5). Thus, at the present time, the high dosage i.v. LMWHs can be best monitored by using the available WB ACT methods. In addition, point-of-care testing to measure the global anticoagulant effect can be carried out using a reliable activated partial thromboplastin time (aPTT) method on whole blood. These results suggest that high dosage of LMWHs is best measured by the global anticoagulant effects, which provide more clinically relevant monitoring.

L10 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:320878 CAPLUS
DOCUMENT NUMBER: 135:220453
TITLE: Emerging anticoagulant and thrombolytic drugs
AUTHOR(S): Iqbal, Omer; Aziz, Salim; Hoppensteadt, Debra A.; Ahmad, Sarfraz; Walenga, Jeanine M.; Bakhos, Mamdouh; Fareed, Jawed
CORPORATE SOURCE: Medical Center, Loyola University Chicago, Maywood, IL, 60153, USA
SOURCE: Emerging Drugs (2001), 6(1), 111-135
CODEN: EMDRFV; ISSN: 1361-9195
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 147 refs. Since its discovery, heparin has been used intensely as an anticoagulant for several medical and surgical indications. However, efforts are in progress to replace heparin because of its serious complications, such as intraoperative and postoperative bleeding, osteoporosis, alopecia, heparin resistance, heparin rebound, heparin-induced thrombocytopenia (HIT) and thrombosis syndrome (HITTS), and other disadvantages. Significant developments in the field of new anticoagulants have resulted in the evaluation and introduction of low mol. wt. heparins (LMWHs) and heparinoids, hirudin, ancrod, synthetic peptides and peptidomimetics. However, despite significant progress in the development of these new anticoagulants, a better or an ideal anticoagulant for cardiovascular patients is not yet available and heparin still continues to amaze both basic scientists and the clinicians. To minimise the adverse effects of heparin, newer approaches to optimize its use in combination with the new anticoagulants may provide better clin. outcome. In our experience, the off-label use of argatroban at a dose of 300 .mu.g/kg iv. bolus followed by 10 .mu.g/kg/min infusion in combination with aggrastat (a glycoprotein [GP] IIb/IIIa **inhibitor**) at a dose of 10 .mu.g/kg iv. bolus followed by an infusion of 0.15 .mu.g/kg/min in patients with HIT undergoing percutaneous coronary interventions resulted in elevation of celite activated clotting time (ACT) to 300 s followed by a gradual decline and the ACT remained above 200 s even after 200 min of drug **administration**. A bewildering array of newer anticoagulants now exist, such as LMWHs and heparinoids, indirect or direct thrombin **inhibitors**, oral thrombin **inhibitors**, such as melagatran (AstraZeneca) and HC-977 (Mitsubishi Pharmaceuticals), **Factor IXa inhibitors**, indirect or direct Factor Xa **inhibitors**, Factor VIIa/tissue factor (TF) pathway **inhibitor**, newer antiplatelet agents, such as GPIIb/IIIa **inhibitors**, fibrin specific **thrombolytic** agent, such as tenecteplase and modulation of the endogenous **fibrinolytic** activity by thrombin activatable **fibrinolytic inhibitor** (TAFI), Factor XIIIa **inhibitors** and PAI-1 **inhibitors**. The quest for newer anticoagulant, antiplatelet and **fibrinolytic**

agents will continue until ideal agents are found.
REFERENCE COUNT: 147 THERE ARE 147 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 3 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001382637 MEDLINE
DOCUMENT NUMBER: 21150141 PubMed ID: 11251339
TITLE: Does inflammation contribute to thrombotic events?.
AUTHOR: Esmon C T
CORPORATE SOURCE: Oklahoma Medical Research Foundation, Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Okla., USA.. Charles-Esmon@omrf.ouhsc.edu
SOURCE: HAEMOSTASIS, (2000) 30 Suppl 2 34-40. Ref: 35
Journal code: FYG; 0371574. ISSN: 0301-0147.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB Recent studies have focused on a myriad of mechanisms by which inflammation can potentiate blood clotting. Inflammatory mediators like endotoxin and tissue necrosis factor (TNF)-alpha can cause the expression of tissue factor on monocytes and, possibly, endothelium, thereby initiating the coagulation cascade. Activation of the complement system can lead to exposure of membrane surfaces capable of amplifying the initial tissue factor stimulus by facilitating the assembly of the factor VIIIa-**factor IXa** and the factor Xa-factor Va complexes. Inflammatory mediators, particularly interleukin-6, can also increase the levels of fibrinogen, an acute-phase reactant. In addition, the inflammatory mediators can elevate the levels of plasminogen activator **inhibitor**, thus suppressing the **fibrinolytic** system. These studies alone, however, do not prove that inflammation can trigger clinically relevant thrombus formation in vivo. For instance, TNF-alpha has been studied in cancer patients as a potential cure for cancer, and even though these patients are hypercoaguable, thrombosis was not commonly observed as a side effect of the near-lethal doses of TNF-alpha that were **administered**. Based on primate studies, inflammatory mediators like TNF-alpha can promote clot deposition effectively only if there is reduced flow and **inhibition** of the natural anticoagulant pathways. The requirement for multiple simultaneous injurious events probably explains why inflammation alone is not observed as a major cause of thrombosis. Copyright 2001 S. Karger AG, Basel

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(FILE 'HOME' ENTERED AT 12:00:48 ON 06 APR 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:01:09 ON 06 APR 2002
L1 12014 S PINSKY D?/AU OR STERN D?/AU OR SCHMIDT A?/AU OR ROSE E?/AU OR
L2 99 S L1 AND (FACTOR (1N) IX)
L3 13 S L2 (P) (FACTOR (1N) IXAI)
L4 6 DUP REM L3 (7 DUPLICATES REMOVED)
L5 2304 S (FACTOR (1N) IXA)
L6 1183 S L5 (P) (INHIBIT? OR INACTIVAT? OR MUTEIN? OR MUTATE? OR ALTE
L7 60 S L6 (P) ADMINIST?
L8 21 DUP REM L7 (39 DUPLICATES REMOVED)
L9 6 S L7 (P) (THROMBOLYTIC OR FIBRINOLYTIC)
L10 3 DUP REM L9 (3 DUPLICATES REMOVED)

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	72.43	72.64
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-6.82	-6.82

STN INTERNATIONAL LOGOFF AT 12:09:40 ON 06 APR 2002